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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,061	06/01/2005	Ira Pastan	4239-67287-05	2145

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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01/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,061	PASTAN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,10-13,21-33,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8,10-13,21-23, 39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 October 2007 has been entered.

2. Claims 5, 7, 9, 14-20 and 34-38 are cancelled.

Claims 1, 4, 6 and 21 have been amended.

Claims 39-40 have been added.

3. Claims 24-33 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-4, 6, 8, 10-13, 21-23 and 39-40 are under consideration.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. This office Action contains New Grounds of Rejections

Rejections Withdrawn

7. The rejection of claims 6, 8 and 10-12 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Fv protein comprising a heavy chain variable region comprising the HCDR1 of residues 31-35 of SEQ ID NO:3, the HCDR2 of residues 50-60 of SEQ ID NO:3 and the HCDR3 of residues 99-107 of SEQ ID NO:3 and a light chain variable region comprising the LCDR1 of residues 157-167 of SEQ ID NO:3, the LCDR2 of residues 183-189 of SEQ ID NO:3 and the LCDR3 of residues 222-230 of SEQ ID NO:3 wherein the Fv protein binds the 8H9 antigen, does not reasonably provide enablement for an isolated Fv protein comprising a heavy chain variable region comprising a complementarity determining region (CDR) that comprises an amino acid sequence of residues 31-35, 50-65 or 99-107 of SEQ ID NO:3

and/or comprising a light chain variable region comprising a CDR that comprises an amino acid sequence of residues 157-167, 183-189 or 222-230 of SEQ ID NO:3 wherein the Fv protein does not bind the 8H9 antigen as broadly encompassed by the claims is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1-3, 6, 8, 10-12 and 21-23 under 35 U.S.C. 103(a) as being unpatentable over Modak et al (Cancer Research, 61:4048-4054, May 15 2001, Ids reference filed 6/1/05) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996) is withdrawn in view of the new grounds of rejections below.

9. The rejection of claims 1-3, 6, 8, 10-12 and 21-23 under 35 U.S.C. 103(a) as being obvious over Cheung [a] (US 2002/0102264 A1, filed 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996) is withdrawn in view of the new grounds of rejections below.

10. The rejection of claims 1-3, 6, 8, 10-12 and 21-23 under 35 U.S.C. 103(a) as being obvious over Cheung [b] (US 2003/0103963 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996) is withdrawn in view of the new grounds of rejections below.

11. The rejection of claims1-3, 6, 8, 10-12 and 21-23 under 35 U.S.C. 103(a) as being obvious over Cheung [c] (US 2005/0169932 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Queen et al (US Patent 5,530,101, issued 6/25/1996) is withdrawn in view of the new grounds of rejections below.

Rejections Maintained and New Grounds of Rejections

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. The rejection of claims 1-4, 6, 8, 10-13, 21-23 and now applied to newly added claims 39-40 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained.

The response filed 10/26/2007 disagrees that monoclonal antibody 8H9 is required to practice the claimed invention, however, in the interest of advancing prosecution the claims are amended to refer to specific heavy and light chains deposited in accordance with the Budapest Treaty. Applicants' arguments have been fully considered but are not found persuasive. The claims still encompass monoclonal antibody 8H9. Claim 6 recites that the Fv binds the same epitope bound by monoclonal antibody 8H9. As presently amended claim 1 recites "an antibody comprising both the variable region of the heavy chain encoded by the nucleic acid molecule deposited in accordance with the Budapest Treaty as ATCC Accession No. PTO-5660 and the variable region of the light chain encoded by the nucleic acid molecule deposited in accordance with the Budapest Treaty as ATCC Accession No. PTA-5661". The claims still encompass monoclonal antibody 8H9, which is merely one interpretation of "an antibody comprising both the variable region of the heavy chain encoded by the nucleic acid molecule deposited in accordance with the Budapest Treaty as ATCC Accession No. PTO-5660 and the variable region of the light chain encoded by the nucleic acid molecule deposited in accordance with the Budapest Treaty as ATCC Accession No.

PTA-5661". Thus, because the VH and VL regions do not convey the complete structure of monoclonal antibody 8H9, and monoclonal antibody 8H9 is required to practice the claimed invention, the rejection is maintained.

Additionally, the examiner acknowledges the previously submitted deposit receipt from the ATCC and a copy of Form PCT/RO/134 that was published with the parent PCT application, however, applicant has not provided the necessary assurances that *all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application.* This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-4, 6-8, 10-13, 21-23 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modak et al (Cancer Research, 61:4048-4054, May 15 2001, Ids reference filed 6/1/05) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994, cited on PTO-892 mailed 2/22/07) and Pastan et al (WO 97/13529, 4/17/1997).

The claims are drawn to a disulfide stabilized immunotoxin comprising an Fv that binds the same epitope as an antibody comprising the 8H9 heavy and light chain variable regions (e.g., encoded by PTA-5660 and PTA-5661) or comprising an Fv comprising the heavy chain 8H9 CDRs (i.e., residues 31-35, 50-65 and 99-107 of SEQ ID NO:3) and the light chain 8H9 CDRs (i.e., residues 157-167, 183-189 and 222-230 of SEQ ID NO:3) wherein the Fv binds the same epitope as monoclonal antibody 8H9 and comprising human heavy and light chain frameworks and a toxin, and wherein the toxin is ricin A, abrin, diphtheria toxin, saporin, restrictocin, gelonin or a subunit of Pseudomonas exotoxin (i.e., PE38, PE40, PE38KDEL or PE38REDL). Further, the claims are drawn to a pharmaceutical composition comprising 0.5 to 15 mg/kg of the disulfide stabilized immunotoxin and a pharmaceutically acceptable carrier.

Modak et al tech the hybridoma that produces murine monoclonal antibody 8H9 that recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues (see entire document). Modak et al do not specifically teach an 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or a humanized 8H9 disulfide-

stabilized-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising 0.5 to 15 mg/kg of the disulfide stabilized immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Pastan et al.

Robinson et al teach Fv derived from a known antibody (see columns 12-22). Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce Fv (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph).

Reiter et al teach disulfide-stabilized immunotoxins (dsFv-immunotoxins) comprising a truncated form of *Pseudomonas* exotoxin (PE38KDEL) that have equal or improved antigen-binding activity compared to their single-chain counterparts, and are easier to produce with high yields and are more stable than single-chain Fv-immunotoxins (scFv-immunotoxins) (see entire document, particularly abstract and pp. 5452, 5457-5458 and Figs. 2, 4-6 and Tables 1-3).

Pastan et al also teach disulfide-stabilized immunotoxins comprising an Fv attached to a *Pseudomonas* exotoxin and having a reduced tendency to aggregate, wherein the heavy and light chain variable regions are cross-linked by the formation of a disulfide bond and may be humanized and Pastan et al teach pharmaceutical compositions comprising the disulfide-stabilized immunotoxins and a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day and the concentration of these formulations can vary widely, and will be selected primarily based on fluid volume, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs (see entire document, particularly pp. 9-13, 20 and 28-29).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Modak et

al and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at a dosage from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Pastan et al because Modak et al tech the hybridoma that produces murine monoclonal antibody 8H9 that recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Pastan et al also teach disulfide-stabilized immunotoxins comprising an Fv attached to a *Pseudomonas* exotoxin and having a reduced tendency to aggregate, wherein the heavy and light chain variable regions are cross-linked by the formation of a disulfide bond and may be humanized and Pastan et al teach pharmaceutical compositions comprising the disulfide-stabilized immunotoxins and a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day and the concentration of these formulations can vary widely, and

will be selected primarily based on fluid volume, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal antibody and produce 8H9 dsFv-immunotoxins including humanized 8H9 dsFv-immunotoxins that are less immunogenic in human tumor patients and since dsFv-immunotoxins are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the 8H9 dsFv-immunotoxins comprising *Pseudomonas* exotoxin in a pharmaceutical composition comprising a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day. Thus, the administration of dosages from 0.1 to about 100 mg is equivalent to administering 8 to 800 mg/kg based on an average weight of 80 kg (176 lbs) for the average human subject in which tumorous disease is treatable. Further, according to the teachings of Pastan et al, the dosage regimen for the dsFv-immunotoxin pharmaceutical composition, including dosage schedule and amount, is a recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of dsFv-immunotoxin pharmaceutical composition and which therefore can be optimized by routine experimentation. See MPEP 2144.05 II.B and *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-

stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Pastan et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [a] (US 2002/0102264 A1, filed 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Pastan et al (WO 97/13529, 4/17/1997).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [a] teaches the hybridoma that produces murine monoclonal antibody 8H9 and antigen-binding fragments of the 8H9 monoclonal antibody including single-chain antibody 8H9 (scFv-8H9) linked to a cytotoxic agent as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 4-6 and Tables 1-4). Cheung [a] does not specifically teach an 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or a humanized 8H9 disulfide-stabilized-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising 0.5 to 15 mg/kg of the disulfide stabilized immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Pastan et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Pastan et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Modak et al and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at a dosage from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Modak et

al and Robinson et al and Reiter et al and Pastan et al because Cheung [a] teaches the hybridoma that produces murine monoclonal antibody 8H9 and antigen-binding fragments of the 8H9 monoclonal antibody including single-chain antibody 8H9 (scFv-8H9) linked to a cytotoxic agent as well as a pharmaceutical composition comprising the scFv-8H9-cytotoxic agent and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Pastan et al also teach disulfide-stabilized immunotoxins comprising an Fv attached to a *Pseudomonas* exotoxin and having a reduced tendency to aggregate, wherein the heavy and light chain variable regions are cross-linked by the formation of a disulfide bond and may be humanized and Pastan et al teach pharmaceutical compositions comprising the disulfide-stabilized immunotoxins and a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day and the concentration of these formulations can vary widely, and will be selected primarily based on fluid volume, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal antibody and produce 8H9 dsFv-immunotoxins including humanized 8H9 dsFv-immunotoxins that are less immunogenic in human tumor patients and since dsFv-immunotoxins are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the 8H9 dsFv-immunotoxins comprising *Pseudomonas* exotoxin in a pharmaceutical composition comprising a pharmaceutically acceptable carrier for administration at dosages from 0.1

to about 100 mg per patient per day. Thus, the administration of dosages from 0.1 to about 100 mg is equivalent to administering 8 to 800 mg/kg based on an average weight of 80 kg (176 lbs) for the average human subject in which tumorous disease is treatable. Further, according to the teachings of Pastan et al, the dosage regimen for the dsFv-immunotoxin pharmaceutical composition, including dosage schedule and amount, is a recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of dsFv-immunotoxin pharmaceutical composition and which therefore can be optimized by routine experimentation. See MPEP 2144.05 II.B and *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Cheung [a] and Robinson et al and Reiter et al and Pastan et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [b] (US 2003/0103963 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Pastan et al (WO 97/13529, 4/17/1997).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [b] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 5-6 and Tables 1-4). Cheung [b] does not specifically teach an 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or a humanized 8H9 disulfide-stabilized-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising 0.5 to 15 mg/kg of the disulfide

stabilized immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Pastan et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Pastan et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Modak et al and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at a dosage from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Pastan et al because Cheung [b] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and

specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Pastan et al also teach disulfide-stabilized immunotoxins comprising an Fv attached to a *Pseudomonas* exotoxin and having a reduced tendency to aggregate, wherein the heavy and light chain variable regions are cross-linked by the formation of a disulfide bond and may be humanized and Pastan et al teach pharmaceutical compositions comprising the disulfide-stabilized immunotoxins and a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day and the concentration of these formulations can vary widely, and will be selected primarily based on fluid volume, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal antibody and produce 8H9 dsFv-immunotoxins including humanized 8H9 dsFv-immunotoxins that are less immunogenic in human tumor patients and since dsFv-immunotoxins are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the 8H9 dsFv-immunotoxins comprising *Pseudomonas* exotoxin in a pharmaceutical composition comprising a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day. Thus, the administration of dosages from 0.1 to about 100 mg is equivalent to administering 8 to 800 mg/kg based on an average weight of 80 kg (176 lbs) for the average human subject in which tumorous disease is treatable. Further, according to the teachings of Pastan et al, the dosage regimen for the dsFv-immunotoxin pharmaceutical composition, including dosage schedule and amount, is a recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of dsFv-immunotoxin pharmaceutical composition and

which therefore can be optimized by routine experimentation. See MPEP 2144.05 II.B and *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Cheung [b] and Robinson et al and Reiter et al and Pastan et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims1-3, 6-8, 10-12 and 21-23 are rejected under 35 U.S.C. 103(a) as being obvious over Cheung [c] (US 2005/0169932 A1, priority to at least 10/18/2001) in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997, cited on PTO-892 mailed 10/13/06) and Reiter et al (Biochemistry, 33:5451-5459, 1994) and Pastan et al (WO 97/13529, 4/17/1997).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Cheung [c] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject (see entire document, particularly pp. 5-6 and Tables 1-4). Cheung [c] does not specifically teach an 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or a humanized 8H9 disulfide-stabilized-immunotoxin comprising the 8H9 CDRs and human frameworks or a pharmaceutical composition comprising 0.5 to 15 mg/kg of the disulfide stabilized immunotoxin and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Robinson et al and Reiter et al and Pastan et al.

Robinson et al have been described supra.

Reiter et al have been described supra.

Pastan et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of Robinson et al to obtain the nucleic acids encoding the VH and the VL from the 8H9 hybridoma taught by Modak et al and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7

and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at a dosage from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have obtained the nucleic acids encoding the VH and the VL from the 8H9 hybridoma and produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Modak et al and Robinson et al and Reiter et al and Pastan et al because Cheung [c] teaches the hybridoma that produces murine monoclonal antibody 8H9 and an 8H9 single-chain antibody (scFv-8H9) linked to a cytotoxic agent, which recognizes a tumor-associated antigen expressed on the cell membranes of a broad spectrum of tumors with restricted distribution on normal tissues as well as a pharmaceutical composition comprising the scFv-8H9 antibody and a pharmaceutically acceptable carrier for inhibiting the growth of tumor cells in a subject and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Reiter et al teach disulfide-stabilized immunotoxins comprising PE38KDEL that have equal or improved antigen-binding activity compared to their single-chain counterparts, are easier to produce with high yields and are more stable than scFv-immunotoxins and Pastan et al also teach disulfide-stabilized immunotoxins comprising an Fv attached to a *Pseudomonas* exotoxin and having a reduced tendency to aggregate, wherein the heavy and light chain variable regions are cross-linked by the formation of a disulfide bond and may be humanized and Pastan et al teach pharmaceutical compositions comprising the disulfide-stabilized immunotoxins and a

pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day and the concentration of these formulations can vary widely, and will be selected primarily based on fluid volume, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known 8H9 monoclonal antibody and produce 8H9 dsFv-immunotoxins including humanized 8H9 dsFv-immunotoxins that are less immunogenic in human tumor patients and since dsFv-immunotoxins are easier to produce with high yields and are more stable than scFv-immunotoxins. In addition, one of ordinary skill in the art would have been motivated to provide the 8H9 dsFv-immunotoxins comprising *Pseudomonas* exotoxin in a pharmaceutical composition comprising a pharmaceutically acceptable carrier for administration at dosages from 0.1 to about 100 mg per patient per day. Thus, the administration of dosages from 0.1 to about 100 mg is equivalent to administering 8 to 800 mg/kg based on an average weight of 80 kg (176 lbs) for the average human subject in which tumorous disease is treatable. Further, according to the teachings of Pastan et al, the dosage regimen for the dsFv-immunotoxin pharmaceutical composition, including dosage schedule and amount, is a recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of dsFv-immunotoxin pharmaceutical composition and which therefore can be optimized by routine experimentation. See MPEP 2144.05 II.B and *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known 8H9 antibody could be established from the 8H9 hybridoma using techniques disclosed in the reference. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have obtained the nucleic acids encoding the

VH and the VL from the 8H9 hybridoma produce a 8H9 disulfide-stabilized-immunotoxin (e.g., comprising SEQ ID Nos:7 and 8) or produce a humanized 8H9 disulfide-stabilized-immunotoxin (hu8H9 dsFv-immunotoxin) as well as a pharmaceutical composition comprising the hu8H9 dsFv-immunotoxin and a pharmaceutically acceptable carrier administered at dosages from 0.1 to about 100 mg per patient per day for therapeutic benefit in human tumor patients in view of Cheung [c] and Robinson et al and Reiter et al and Pastan et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

With respect to each of the above obviousness rejections (which only differ with respect to the primary reference), the response filed 10/26/2007 submits a second Declaration of Dr. Pastan under 37 C.F.R. 1.132, which documents the unexpectedly superior properties of the 8H9 dsFv linked to a toxin (PE38) as compared to the 8H9 scFv linked to PE38. The declaration documents the unexpected finding that the 8H9 dsFv showed substantially less toxicity than the scFv form, which according to applicant could not have been predicted based on the teachings of the cited prior art. Applicants' arguments and the second Declaration of Dr. Pastan under 37 C.F.R. 1.132 have been carefully considered but are not found persuasive. The examiner agrees that the unexpected findings of the 8H9 dsFv compared to the 8H9 scFv with which applicant argues could not be predicted based on the cited prior art, however, applicant is reminded that the present rejections are based on the art recognized advantages that dsFv-immunotoxins are obtained in increased yields due to a decreased tendency of properly folded dsFv-immunotoxins to aggregate and dsFv-immunotoxins are easier to produce with high yields and are more stable than scFv-immunotoxins and dsFv-immunotoxins (and dsFvs alone) might be more useful than scFv's in clinical and other applications that require large amounts of stable recombinant Fv's (Reiter et al, see pg.

5455, 5458 and abstract). Applicants' reliance upon the unexpected finding that the 8H9 dsFv showed substantially less toxicity than the scFv form is not found persuasive because "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). See MPEP 2145.

Further, applicants' arguments and evidence that the 8H9 dsFv showed substantially less toxicity than the scFv form are curious in view of certain evidence in the previously submitted Declaration of Dr. Pastan under 37 C.F.R. 1.132 (filed 5/21/07), the evidence in the specification at pg. 47 (Table 1) and Onda et al (Cancer Research, 64:1419-1424, February 15, 2004, IDS reference filed 11/10/05), all of which demonstrate that 8H9 dsFv-PE38 showed cytotoxic and antitumor activities *similar to those* of 8H9 scFv-PE38, was well tolerated in monkeys and a dose that causes significant tumor regression in mice is well tolerated by monkeys.

For these reasons and those already of record, the above obviousness rejections under 35 U.S.C. 103(a) are maintained.

19. The provisional rejection of claims 1-3, 6, 8, 10-13, 21-23 and now applied to newly added claims 39-40 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 6-7, 9, 11 and 52-54 of copending

Application No. 10/097,558 in view of Reiter et al (Biochemistry, 33:5451-5459, 1994, cited on PTO-892 mailed 2/22/07) is maintained.

The response refers to the Declaration of Dr. Pastan as documenting the non-obviousness of the presently claimed invention and applicant requests that this rejection be held in abeyance until allowable subject matter is identified. Applicants' arguments and the Declaration of Dr. Pastan have been fully considered but are not found persuasive in view of the examiners above remarks regarding the obviousness rejection. Further, in view that no terminal disclaimer has been filed, the rejection is maintained.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/097,558, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

20. The provisional rejection of claims 1-3, 6, 8, 10-13, 21-23 and now applied to newly added claims 39-40 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6-10 of copending Application No.

10/505,658 in view of Reiter et al (Biochemistry, 33:5451-5459, 1994, cited on PTO-892 mailed 2/22/07) is maintained.

The response filed 10/26/20007 does not address the rejection and the rejection is maintained for reasons already of record.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 10/505,658, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Claim Objections

21. Claim 1 is objected to because in the recitation "PTO-5660" which appears to be a typo and should be corrected to PTA-5660.

Appropriate correction is required.

22. Claims 1 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 recites the limitation "wherein the variable region of the heavy chain and the variable region of the light chain" (last few lines of the claim). There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites the heavy and light chain variable region of a monoclonal antibody and the heavy and light chain variable regions encoded by the nucleic acids deposited as PTA-5660 and PTA-5661, making it unclear which heavy and light chain variable regions are being referenced by the claims. See MPEP 2173.05(e).

b. Claims 39 and 40 are indefinite in the recitation "does not produce toxicity in a subject" as the exact meaning of the phrase is unclear. The claims are directed to a pharmaceutical composition comprising a dsFv-immunotoxin wherein the toxin moiety of the immunotoxin is toxic to the target cells as disclosed in the specification. Thus, it is unclear what is contemplated by the phrase "does not produce toxicity in a subject". Does the phrase mean that the immunotoxin is not toxic to the target cells, or does the immunotoxin not elicit an immune response in a subject (e.g., human anti-mouse antibody response; HAMA) or is some other meaning contemplated by the phrase? As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

23. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Fv polypeptide comprising the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and an effector molecule wherein the Fv polypeptide binds the same epitope as the 8H9 monoclonal antibody, does not reasonably provide enablement for an isolated Fv polypeptide comprising an amino acid sequence set forth as SEQ ID NO:7 and an amino acid sequence set forth as SEQ ID NO:8 and an effector molecule wherein the Fv polypeptide binds the same epitope as the 8H9 monoclonal antibody as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is drawn to engineered antibodies, where the relative skill of those in the art is deemed to be high.

The claim is drawn to an isolated Fv polypeptide comprising an amino acid sequence set forth as SEQ ID NO:7 and an amino acid sequence set forth as SEQ ID NO:8 and an effector molecule wherein the Fv polypeptide binds the same epitope as the 8H9 monoclonal antibody. The phrase "comprises an amino acid sequence" reads upon fragments of the recited variable domain sequences, since a fragment comprising two amino acids of SEQ ID NO:7, for example, is merely one interpretation of "an amino acid sequence set forth as SEQ ID NO:7". Thus, the claims broadly encompass isolated Fv proteins that do not contain all six CDRs of monoclonal antibody 8H9, three from the heavy chain variable domain and three from the light chain variable domain and do not bind the 8H9 antigen.

The specification discloses only Fv polypeptides/antibodies comprising all six CDRs from the 8H9 monoclonal antibody (see Examples). The specification does not teach Fv polypeptides/antibodies that do not contain all six CDRs from the 8H9 monoclonal antibody and wherein the Fv polypeptides/antibodies bind the 8H9 antigen. There are no working examples of Fv polypeptides/antibodies that do not contain all six CDRs from the 8H9 monoclonal antibody and wherein the Fv polypeptides/antibodies bind the 8H9 antigen. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 1924 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of most antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions", cited on PTO-892 mailed 2/22/07). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, 1982, cited on PTO-892 mailed 2/22/07). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that an isolated Fv protein, which contains less than the full complement of CDRs from the 8H9 heavy and light chain variable regions in their proper order and in the context of framework sequences which maintain the correct spatial orientation for antigen recognition have the required 8H9 binding function. There is insufficient guidance and direction to assist those skilled in the art in using Fv proteins comprising fragments of the recited 8H9 variable region sequences (i.e., "an amino acid sequence"), wherein the Fv polypeptides/antibodies bind the 8H9 antigen. One of skill in the art could not predictably extrapolate the teachings of the specification limited to 8H9 Fv antibodies that comprise all six CDRs from the 8H9 monoclonal antibody and bind 8H9 to Fv proteins comprising fragments of the recited 8H9 heavy and/or light

chain variable regions (i.e., "an amino acid sequence"), wherein the Fv protein binds 8H9. One of skill in the art would neither expect nor predict the appropriate functioning of the Fv polypeptides as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul and Rudikoff et al, the lack of guidance and direction in the specification, and the absence of working examples, undue experimentation would be required to practice the claimed Fv polypeptides that bind the 8H9 antigen with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed Fv polypeptides and absent working examples providing evidence which is reasonably predictive that the claimed Fv polypeptides, which contain less than the full complement of CDRs from the 8H9 heavy and light chain variable regions in their proper order and in the context of framework sequences have the requisite 8H9 binding function, commensurate in scope with the claimed invention.

24. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643